REMARKS

Claims 1-7 and 15-31 are pending. A copy of the currently pending claims is appended hereto as Appendix A.

Response to Rejection Under 35 U.S.C. § 112

Claims 1-7 and 15-31 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner states that "[t]he presently pending claims only require that the substrate have discrete sites, over which the random microsphere distribution occurs, and lack the limitation that these discrete sites are "patterned," and "this broadening of the practice of the sites on the substrate surface compared to the written support as pointed out by applicants for the microsphere distribution and its surface is NEW MATTER." Applicants respectfully traverse.

As stated in MPEP § 2163.06, "information contained in any one of the specification, claims or drawings of the application as filed may be added to any other part of the application without introducing new matter," and "[t]he claims as filed in the original specification are part of the disclosure."

The Examiner notes that "Applicants arguments are replete with the acknowledgment that the invention is directed to the random distribution of microspheres on a patterned substrate or on a patterned surface of discrete sites."

However, as Applicants noted in the previous response to Office Action mailed May 2, 2000, "the specification is describing that the sites on the surface of the substrate may be arranged in a pattern or may be random," and "[a]s noted by the Examiner, at p.10, line 7, the "sites may be a pattern...or randomly distributed." Moreover, Applicants reiterate that the section, i.e., p.9, line 30 to p.10 line 17 of the specification, indicates that the substrate may

contain patterned sites or alternatively it may contain random distribution of sites; however, this section does not describe the manner in which microspheres are distributed on the surface.

Instead, random distribution of microspheres is disclosed elsewhere, i.e., at p.6, line 21-30 of the specification, which says, "the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art."

Therefore, Applicants respectfully submit that the specification as filed contains written support regarding random distribution of microspheres onto a substrate surface that may have patterned discrete sites or randomly distributed discrete sites.

Furthermore, the claims as originally filed do not limit the discrete sites on a substrate surface to be patterned.

Accordingly, Applicants respectfully submit that no NEW MATTER has been introduced and the currently pending claims are allowable under 35 U.S.C. § 112. Applicants respectfully request the Examiner to withdraw this rejection.

Response to Rejection Under 35 U.S.C. § 102

Claims 1, 3-5, 7, 15, 16, 18-22, and 25-31 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Walt et al. (U.S. Patent No. 6,023, 540).

As the Examiner is aware, "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Walt et al. is directed to a microsphere-based analytic chemistry system in which microspheres carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality on each bead using an optically interrogatable encoding scheme. Walt et al. elegantly present two synergistic inventions, which, when implemented together, yield a biosensor that supports large numbers of separate chemical functionalities and is easier to manufacture and use than previous methods of building on the sensor's end various

chemical functionalities in a serial fashion. Nevertheless, Walt et al. relies on a system of optical signature encoding of the biosensor and is silent with respect to identifier binding ligands and decoding binding ligands.

Claims 1 and 7 in this application are directed to an array composition and a method of making this array composition, respectively, that comprise random distribution of microspheres containing a bioactive agent and an identifier binding ligand onto a surface with discrete sites. Claims 22 and 25 are directed to a composition and a method of making this composition, respectively, that comprise randomly distribution of microspheres containing a bioactive agent, an identifier binding ligand and a decoder binding ligand onto a surface with discrete sites. Each of these independent claims recites that the microspheres contain a bioactive agent and an identifier binding ligand. In contrast, Walt et al. is silent with respect to identifier binding ligands.

The Examiner asserts that Walt et al. anticipates the decoder binding ligand limitation, because Walt et al. discloses that "the optical response of the microspheres is changed as a result of binding of entity "64", for example a fluorescent dye, to the microspheres." Applicants respectfully traverse.

Applicants submit that binding of entity "64" to the microspheres in Walt et al. in no way anticipates the decoder binding ligand limitation in the present invention, for example claim 3. As illustrated in column 10, line 50-60 in Walt et al., observation of a fluorescent marker dye 64 on the microspheres only determines that at least one of the target sequences is present, but cannot determine, i.e., decode, which probe sequence is generating the activity. Thus, Walt et al. is silent with respect to decoder binding ligands. Rather, Walt et al. determines which microspheres contains which probe sequence by encoding each microsphere in each subpopulation sharing a common probe sequence with a common optical signature such as the combination of a specific ratio of reporter dyes, as elucidated in column 10, line 61-67. Therefore, Walt et al. does not anticipate the element of decoder binding ligand in the present invention.

Accordingly, Applicants submit that Walt et al. does not anticipate the presently pending claims.. Applicants respectfully request the Examiner to withdraw this rejection.

Claims 1, 4, 5, 7, 18, 20, 30 and 31 are rejected under 35 U.S.C. § 102(b) and (e) as being clearly anticipated by Ekins et al. (U.S. Patent No.5,516,635).

As noted above, "for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc., supra.*

Ekins et al. teaches a binding assay process for an analyte using a capture binding agent with binding sites specific for the analyte and a developing binding material capable of binding with the bound analyte or with the binding sites on the capture binding agent either occupied by the bound analyte or the remaining unoccupied binding sites.

As the Examiner notes, "[w]hen the microspheres of Ekins et al. are applied to the surface they are in a solution which permits their random movement to the surface and attachment wherever they encounter a binding entity which is recognized by one of said antibodies." The Examiner suggests that Ekins et al. anticipates the claims because the beads in Ekins et al. move randomly in solution to the surface. Applicants respectfully traverse.

Claims 1 and 7 in this application are directed to an array composition and a method of making this array composition, respectively, that comprise random distribution of microspheres containing bioactive agents and identifier binding ligands onto a surface with discrete sites.

As disclosed in the specification as filed, p. 6, line 30-32, "the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art." Thus, the present invention, in this important aspect, is distinct from prior art such as Ekins et al that requires a process to spot "binding entity" on a surface first.

That is, Applicants respectfully submit that "random movement to the surface" of Ekins et al. does not equal random distribution onto a surface. As the Examiner notes, the

attachment of microspheres in Ekins et al. occurs "wherever they encounter a binding entity." Thus, the distribution is not random. In fact, random distribution of microspheres onto a surface would completely defeat the purpose of the binding assay system described in Ekins et al.

Furthermore, Ekins et al. does not teach or suggest identifier binding ligands at all.

Accordingly, Applicants submit that Ekins et al fails to anticipate each element of the claims.

The Examiner also notes that "the remaining claim limitations directed to nucleic acid or protein binding agents are disclosed in Ekins et al.," and "Ekins et al. also cites several types of markers or labels...[and discloses] solid supports, such as specifically described plastic walls of microtitre plates." However, Applicants respectfully submit that "the remaining claim limitations" are disclosed in claims 4, 5, 30, and 31 that are dependent on allowable independent claims.

Therefore, Ekins et al does not anticipate every element of the present invention. Accordingly, the claims at issue are allowable under 35 U.S.C. § 102; Applicants respectfully request the Examiner to withdraw the rejection.

Response to Rejection under 35 U.S.C. § 103

Claims 1-7, 18, 20, and 22-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ekins et al. (U.S. Patent No. 5,516,635); taken in view of Matthews et al.

Ekins et al. is discussed above.

Matthews et al. is a review that "describe[s] the various labels and strategies for DNA probe assays," at p.1, column 1, para. 1. Matthews et al. teaches a variety of DNA probe assays that utilize direct labeling of DNA probes with radioactive, fluorescent or enzyme labels. This review also teaches indirect procedures in DNA probe assays including the usage of proteins that specifically interact with a nucleic acid duplex.

The Examiner suggests that "Ekins et al describes the basic microsphere and array invention as instantly claimed but does not disclose the usage of a bound decoder ligand nor a non-labeled microsphere."

The Examiner further notes that Ekins et al. describes "the usage of enzyme markers or labels," and Matthews et al. teaches that "enzymes are well known as being attachable to biomolecules for subsequent development with a substrate which result in a label which is the actually detected entity." The Examiner asserts that "these substrate usages may be interpreted as decoder ligands which are bound to the immobilized microspheres after ligand detection via their attached antibody," and "[t]his interpretation suggests and motivates a reasonable interpretation of the decode ligand binding limitations of the instant claims." Applicants respectfully traverse.

Applicants note that there are three requirements to establish a prima facie case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (MPEP § 2143).

Based on Ekins et al., taken in view of Matthews et al., a person of ordinary skill in the art may employ the enzymes described in the latter to label microspheres used in an Ekins et al. binding assay and add the respective substrates of the enzymes to obtain detectable signals. As the Examiner notes, Ekins et al. does not provide any motivation to employ binding of a decoder binding ligand to an identifier binding ligand in a microsphere-based assay system. Neither does Matthews et al. provide any motivation to employ the described DNA probes including the enzyme-substrate systems as an identifier binding ligand or a decoder binding ligand in a microsphere-based system.

Moreover, Ekins et al. in light of Matthews et al. does not provide motivation for the combination of the references to employ an array composition and a method of making such a

composition by random distribution of microspheres onto a surface with discrete sites, because the binding assays utilizing labeled microspheres in Ekins et al. rely on a form of specific interaction between a developing binding material and a capture binding agent or an analyte.

In addition, Applicants submit that even assuming, arguendo, that there is motivation, Ekins et al. in light of Matthews et al. does not lead to the compositions and methods in claims 1-7, 18, 20, and 22-31. That is, the skilled artisan would not have a reasonable expectation of practicing the invention as claimed.

Ekins et al. does not teach or suggest random distribution of labeled microspheres onto a surface with discrete sites at all. A random distribution of the labeled microspheres onto different microspots bound by different capture binding agents would completely defeat the purpose of the assay in Ekins et al. Moreover, Ekins et al. does not teach or suggest a composition or a method to employ identifier binding ligands.

Figures 3-5 in Ekins et al. further support Applicants' contention that Ekins et al. does not teach random distribution of microspheres. In each of these figures, a microsphere M is shown to bind to a capture binding agent B immobilized by a microspot A. The interaction between capture binding agent and developing binding material conjugated to microspheres in Ekins et al. is of a specific nature. As such, the distribution of microspheres is not random.

Therefore, Ekins et al. does not provide a reasonable expectation of practicing the present invention by random distribution of microspheres onto a surface with discrete sites.

Finally, Applicants submit that Ekins et al. fails to teach or suggest all the claim limitations. Because this application employs a composition comprising identifier binding ligands and a method of making such a composition by randomly distributing microspheres onto a surface with discrete sites, Ekins et al. does not teach or suggest all the claim limitations in this application.

Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Applicants respectfully request the Examiner to withdraw the rejection.

Response to Provisional Rejection under the Double-Patenting Doctrine

Claims 1-7 and 15-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending application Serial No. 09/473,904.

As the Examiner may be aware by now, claims 1-11 of copending application Serial No. 09/473,904 have been cancelled in response to the restriction requirement mailed January 17, 2001.

Accordingly, Applicants respectfully submit that this provisional rejection is moot and should be withdrawn.

Applicants submit that the claims as amended are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

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APPENDIX A: CURRENTLY PENDING CLAIMS

1. An array composition comprising:

a) a substrate with a surface comprising discrete sites at a density of at least 100 sites per 1 mm^2; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and said second subpopulations comprise:

i) a first and second bioactive agent, respectively; and

ii) a first and second identifier binding ligand, respectively;

wherein said microspheres are randomly distributed on said surface.

2. An array composition comprising:

a) a substrate with a surface comprising discrete sites at a density of at least 100 sites per 1 mm^2; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and second bioactive agent, respectively, and do not comprise a label, wherein said microspheres are randomly distributed on said surface.

3. A composition according to claim 1, 2 or 17, further comprising at least one decoder binding ligand.

4. A composition according to claim 1, 2, 17, 22 or 23, wherein said bioactive agents are nucleic acids.

5. A composition according to claim 1, 2, 17, 22 or 23, wherein said bioactive agents are proteins.

6. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and a second bioactive agent, respectively, and do not comprise a label.

7. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulatio, wherein said first and second subpopulations comprise:

i) a first and second bioactive agent, respectively; and

ii) a first and a second identifier binding ligand.

15. The composition according to claim 1, 2, 17, 22 or 23, wherein said discrete sites are wells.

16. The method according to claim 6, 7, 24 or 25, wherein said discrete sites are wells.

17. An array composition comprising:

a) a substrate with a surface comprising discrete sites, wherein said substrate is a fiber optic bundle; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein each subpopulation comprises a bioactive agent and does not comprise a label, wherein said microspheres are randomly distributed on said surface.

18. A composition according to claim 1, 2, 22 or 23, wherein said substrate is selected from the group consisting of glass and plastic.

19. A composition according to claim 1, 2, 22 or 23, wherein said substrate is a fiber optic bundle.

20. A method according to claim 6, 7, 24 or 25, wherein said substrate is selected from the group consisting of glass or plastic.

21. A method according to claim 6, 7, 24 or 25 wherein said substrate is a fiber optic bundle.

22. An array composition comprising:

a) a substrate with a surface comprising discrete sites; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and second subpopulations comprise:

i) a first and a second bioactive agent, respectively;

ii) a first and second identifier binding ligand, respectively; and

iii) a first and a second decoder binding ligand, bound to said first and second identifier binding ligands, respectively;

wherein said microspheres are randomly distributed on said surface.

23. An array composition comprising:

a) a substrate with a surface comprising discrete sites; and

b) a population of microspheres comprising:

i) at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and a second bioactive agent, respectively, and do not comprise a label; and

ii) a first and a second decoder binding ligand bound to said first and second bioactive agent, respectively;

wherein said microspheres are randomly distributed on said surface.

24. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation comprising a first and second bioactive agent, respectively; and

c) binding a first and second decoder binding ligand to said first and second bioactive agent, respectively;

wherein said microspheres do not comprise a label.

25. A method of making a composition comprising:

a) forming a surface comprising individual sites on a substrate;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulations, wherein said first and second subpopulations comprise:

i) a first and second bioactive agent, respectively; and

ii) a first and second identifier binding ligand, respectively,

c) binding a first and second decoder binding ligand to said first and second identifier binding ligand.

26. A method according to claim 6 further comprising:

c) binding a first and second decoder binding ligand to said first and second bioactive agent.

27. A method according to claim 7 further comprising:

c) binding a first and second decoder binding ligand to said first and second identifier binding ligand.

28. A method according to claim 24, 25, 26 or 27, wherein at least said first decoder binding ligand comprises a label.

29. A composition according to claim 3, wherein said at least one decoder binding ligand comprises a label.

30. A composition according to claim 1, wherein said first bioactive agent is said first identifier binding ligand.

31. A method according to claim 7, wherein said first bioactive agent is said first identifier binding ligand.